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TOBACCO INDUSTRY RESEARCH COMMITTEE  
350 FIFTH AVENUE NEW YORK 1, N. Y.

*Interesting  
Prob. valuable  
Assumed missing OK*  
Application For Research Grant

Date: October 8, 1954

1. Name of Investigator: *A* William W. Wolff, A.M., Ph.D.

2. Title: Associate Professor of Clinical Chemistry and Toxicology

3. Institution & Address: Bowman Gray School of Medicine  
South Hawthorne Road, Winston-Salem, N. C.

4. Project or Subject: A: The Fate of Tars from Cigarette Smoke Deposited in the Dog Lung  
B: Cigarette Smoke in the Human Lung, a Radioisotope Study

5. Detailed Plan of Procedure (Use reverse side if additional space is needed)

A: By means of carbon-14 as an isotope tracer, an extensive experimental study will be made on the deposition and removal of tar components of cigarette smoke deposited in the dog lung. This will be a continuation of studies now being completed. (See statement below.)

A study is planned in three phases. The first phase will be the development of an economical and efficient method for introducing a carbon-14 label into tar constituents of cigarette smoke. Following the technique used in our studies with other isotopes, various types of organic compounds labeled with carbon-14 will be introduced into the cigarette just prior to smoking. The smoke from the treated cigarette will be condensed in a flask cooled with dry ice and the carbon-14 activity of the tar will be measured. Various procedures will be used to determine the nature of the carbon-14 linkage in the tar. As a second method, compounds such as glucose or amino acids containing carbon-14 will be introduced as a nutrient solution into the green tobacco leaf which will then be processed into cigarettes. The latter method should give a "true label" by actually incorporating carbon-14 atoms into normal constituents of the tobacco. This part of the study might throw light on the mechanism of tar formation.

The second phase of the study will be acute smoking experiments with dogs. The pattern of tar deposition in the lung will be determined. Removal of tar from the lungs will be studied as to (a) rate in each area (alveoli versus large bronchi, etc.,) (b) pathway of removal and (c) distribution in other body tissues. The metabolism of carbon-14 labeled tars introduced into the lung will be followed in considerable detail.

The third phase of the study will be long term smoking experiments extending over weeks or months. By using a recently reported technique for introducing a plastic tracheal cannula which remains in place for months, it will be possible to give a dog several doses of smoke for an extended period of time. This program will, to a considerable degree, simulate the pattern of smoking in the human. A study of the metabolism of cigarette smoke tar in the dog under these conditions should suggest the course of events in the human smoker.

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B: The deposition and fate of cigarette smoke in the human lung will be studied by means of radioactive iodine - 131 as a tracer in smoke. Expected results should give new and unique information on (a) the pattern of deposition of smoke particles in the bronchial tree, and (b) the speed at which the smoke deposit leaves the lung.

The feasibility of such experiments has been demonstrated by extensive observations on the dog. The amount of isotope appearing in the smoke, in any dose between 1 and 100 microcuries, can be fixed by the amount of radioactive iodine - 131 as potassium iodide added to the cigarette prior to smoking. Over 90% of the activity (smoke particles?) disappears from the dog lung within a few seconds after the smoke is deposited. The remainder of the radioactive material leaves the lung over a period of 30 to 60 minutes. A somewhat similar result may be expected in the human.

Subjects in this study will be patients undergoing a test of thyroid function under the care of J. Robert Andrews, M.D., Director of the Department of Radiology, N. C. Baptist Hospital. The subject will inhale cigarette smoke containing 50 to 100 microcuries iodine-131. The deposition of radioactive material in the lung and its rapid phase of removal will be measured by a scintillation counter and a high speed scaler on which readings will be made at one or two second intervals during the smoking period by photographing the scaler dials and interpolation lights. At the end of the smoking period the pattern of smoke deposit, the residual radioactivity in the lungs, will be mapped by scanning the entire lung field with the counter collimated to record only a 3 to 5 cm<sup>2</sup> area at each reading. (Chest plates will be obtained for comparison.) Repeated readings over a single area for an hour or more will indicate the speed at which the residual deposit leaves the lungs.

Application for authorization to make this study is being filed with the Atomic Energy Commission by Dr. J. Robert Andrews as clinician-in-charge.

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Enclosed with Dr. Wolff's application were the following, which are in our Scientific Files:

1. "The Effect of Tobacco on Estrus, Pregnancy, Fetal Growth, and Lactation" by Rowland V. Long, M.D., Lexington, N.D.; and William A. Wolff, Ph.D., Winston-Salem, N.C.
2. "Radioautographic method for studying deposition of cigarette smoke in the dog lung" by William A. Wolff, James G. Tuttle and John M. Godfrey
3. "The Use of Radioisotopes as Tracers in Cigarette Smoke" by William A. Wolff, Ph.D., E. G. Purdom, Ph.D. and J. A. Isenhower, B.A.
4. "Studies on tobacco chewing" by William A. Wolff and W. E. Giles
5. "The Spectrophotometric Estimation of Nicotine in Blood" by William A. Wolff, Marina A. Hawkins and W. E. Giles
6. "Nicotine in Blood in Relation to Smoking" by William A. Wolff, Marina A. Hawkins and W. E. Giles

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6. Budget Plan: one year, from 1-1-55 thru 12-31-55

request consideration of grant  
as initial support on long term  
program.

Salaries  
Expendable Supplies incl. C-14 cpds.  
Permanent Equipment  
Overhead  
Other alterations

\$13,000.00
6,000.00
2,000.00
2,000.00
2,000.00
Total \$25,000.00

7. Anticipated Duration of Work:

Project A - 3 to 5 years. Project B - 18 to 24 months.

8. Facilities and Staff Available:

Isotope laboratory, A.E.C. approved, 900 ~~XXXX~~ square feet, 5 rooms, 2 hoods, air conditioned

Chemical laboratory, 550 sq. ft., 2 rooms used for tobacco research only.

Staff: William A. Wolff, Biochemistry (part time)

E. G. Purdon, Ph.D. in physics, electronics and instruments (part time)

J. Robert Andrews, M.D., Clinician-in-charge of human subjects, Project B

Two technicians, chemical (full time)

X-ray technician, photographer and resident in radiology (part time as needed)

9. Additional Requirements:

- (1) Heavy lead shield for scintillation counter
- (2) Time interval movie camera for high speed recording on scaler
- (3) Rebuild one room in animal quarters to accommodate dogs receiving carbon-14 compounds over long periods of time.

10. Additional Information (Including relation of work to other projects and other sources of supply):

The projects proposed above are a direct continuation of a research program which was started in 1944 and has been subsidized in its entirety by the R. J. Reynolds Tobacco Company through its agent, Wm. Esty, Inc. of New York City. During the early years of the program attention was directed to the development of suitable micro methods for a study of nicotine metabolism in the human smoker subject. Investigations on methods and blood nicotine levels in relation to smoking have been published. A study of nicotine absorption from chewing tobacco and a study on the ~~xxx~~ nicotine content of breast milk have been reported but not yet published.

Since April 1951 all effort has been concentrated on a study of isotopes as tracers in cigarette smoke. One paper has been published, two others have been reported, and a third is being completed at the present time. Results obtained to date show that, with a smoke dose and a smoking rate similar to that used by the human smoker, 90 to 98% of the nicotine in the smoke deposit disappears from the dog lung during the period of smoking and the remainder leaves the lungs during the next 30 to 60 minutes. Radioactive sodium or potassium introduced with the smoke leaves the dog lung almost instantly while radioactive iodine and arsenic are removed in about the same manner as is nicotine.

These ~~experiments~~ experiments with radio isotopes have been made on dogs with the object of getting fundamental information on the physiology of smoking.

Signature /s/ William A. Wolff  
Director of Project

/s/ Harry O. Parar  
Business Officer of the Institution

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